

Mansoura Clinical Pharmacology

2015
Simplified
approach

For Medical students

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By
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2015
update

Volume 2

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Chapter 4 | Cardiovascular Pharmacology

Part 1: Systemic Hypertension and Antihypertensive Drugs

Some physiology and pathophysiology

Vascular smooth muscle contraction and relaxation

Vasoconstriction is initiated by opening of voltage gated L-type Ca^{2+} channels in the membrane of vascular smooth muscle cells. Increased intracellular Ca^{2+} triggers the phosphorylation of myosin light chain kinase which initiates contraction.

Vasodilation is initiated by either:

- Activation of guanylyl cyclase $\rightarrow$ $\uparrow$ cGMP $\rightarrow$ dephosphorylation of myosin light chain kinase $\rightarrow$ smooth ms relaxation.
- Opening of K^{+} channels in the vascular smooth muscle cell membrane $\rightarrow$ smooth ms stabilization (hyperpolarization) $\rightarrow$ relaxation.

The vascular endothelium and local vasomotor control

Beside the neural control of blood vessels through the sympathetic and parasympathetic systems, the vascular endothelium produces various compounds that help controlling the vascular tone:

Auton
homic*

Nitric oxide
(NO; or EDRF)

It is a diffusible gas with very short half-life. It causes VD by increasing intracellular cGMP. It protects against atherosclerosis, high blood pressure, heart failure and thrombosis.

()*

PGI₂

It is synergistic to NO. It causes VD via specific receptors

()*

Endothelin

Is a 21-amino-acid peptide. By its action on ET_A receptors, it causes severe VC and vascular smooth muscle hypertrophy.

Angiotensin-converting enzyme (ACE)

Located on the endothelial cell membrane and converts circulating angiotensin-I (synthesized by the action of renin on angiotensinogen) to angiotensin-II. By its action on AT_1 receptors, Ang-II causes VC and stimulates aldosterone release.

()*

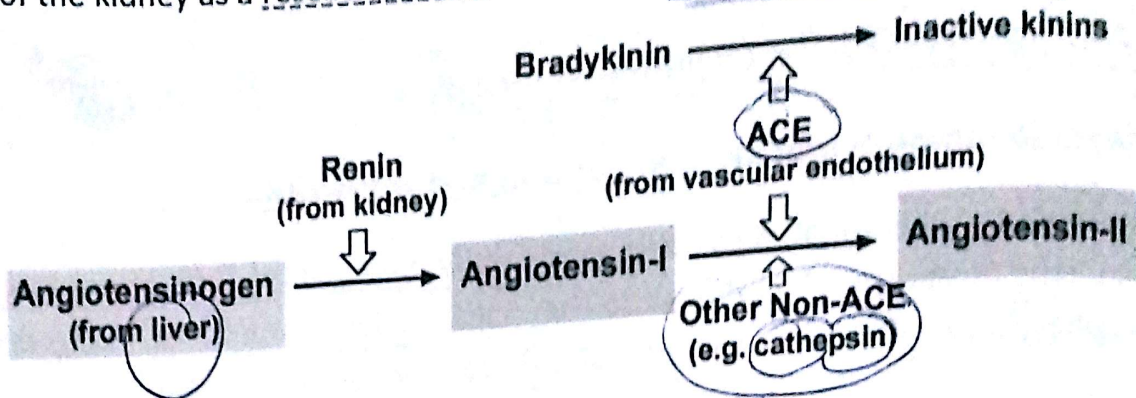
Other factors

Histamine (from mast cells) causes VD, bradykinin (synthesized from kininogen) causes VD, and serotonin (released by platelets) causes VC.

Antacids

The renin-angiotensin-aldosterone (RAAS) system

- When renal ischemia occurs, there is $\downarrow$ RBF and $\downarrow$ GFR. This may lead to acute oliguria that may develop to acute tubular necrosis.
- As a compensatory mechanism, renin is released from the juxtaglomerular cells of the kidney as a rescue message to initiate stimulation of RAAS as follows:



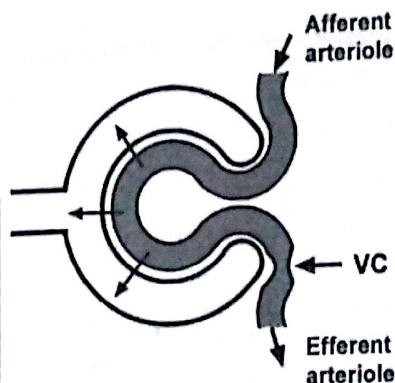
- Ang-II acts on AT1 receptors in the efferent arterioles of the kidney causing their VC and thus maintains adequate GFR in spite of the $\downarrow$ RBF.
- Unfortunately, Ang-II acts on AT1 receptors in other vascular beds and tissues causing systemic VC, cell hypertrophy, and apoptosis (i.e. degenerative changes).

AT1 receptors

Selective VC of the efferent arterioles $\rightarrow$ $\uparrow$ glomerular filtration pr and maintains adequate GFR in spite of the existing renal ischemia.

Systemic VC $\rightarrow$ $\uparrow$ BP
 $\uparrow$ ADH release
 $\uparrow$ aldosterone release

Myocyte hypertrophy
 $\uparrow$ collagen synthesis
 Apoptosis



Preserve renal function in mild ischemia

Hypertension

Remodelling

AT2 receptors

Weak VD
 $\downarrow$ cell proliferation
 Apoptosis

Should you inhibit the RAAS or not?!

- Remember that inhibition of the RAAS will correct hypertension but also will $\downarrow$ GFR and aggravate RF if renal ischemia was grave (i.e. S. creatinine is > 3 mg/dl).
- So, if SCr is up to 3 mg/dl (mild renal impairment) $\rightarrow$ you can safely block RAAS.
- If SCr > 3 mg/dl (severe renal impairment) $\rightarrow$ blocking the RAAS will aggravate RF.

Drugs affecting systemic vascular resistance

Angiotensin-converting enzyme inhibitors (ACEIs)

Classification

- SH-containing drugs: Captopril, zofenopril, alacepril
- Non SH-containing drugs: Enalapril, fosinopril, lisinopril, benazepril, ramipril

Pharmacological properties of some ACEIs

	Captopril	Fosinopril	Enalapril	Lisinopril	Benazepril
SH group	✓ +	-	-	-	-
Immune S/E	✓ +	-	-	-	-
Prodrug	-	* + *	* + *	-	* + *
Metabolism	Liver, kidney	Liver, kidney	Liver	* No metabolism	Liver, kidney
Onset	1-4 h				
Frequency of administration	✓ Short / 8 h	/ 12 h	/ 12 h	/ 24 h	Long duration / 24 h
SL dose	25 mg	None	None	None	None

Mechanism of action

They inhibit **Ang-converting enzyme (ACE)** in the **vascular endothelium** leading to:

- Inhibition of both **Ang-II formation** and **aldosterone release** (→ ↓ both VC and salt & water retention).
- Prevent degradation of **bradykinin** which is a potent VD.
- Most ACEIs have **direct VD action** to both **arteries** (i.e. ↓ afterload) and **veins** (i.e. ↓ preload).

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Pharmacological effects

CVS:

- They ↓ BP mainly by decreasing peripheral resistance but no reflex tachycardia or changes in the COP can occur. This may be due to either (1) resetting of baroreceptors; and/or (2) enhanced parasympathetic activity.

- They ↑ COP (only in presence of CHF) due to reduction of both venous return (preload), and systemic BP (afterload).

- They ↓ myocardial changes complicating acute myocardial infarction (ventricular hypertrophy, dilatation, and dense collagen scar) because they prevent myocyte cell hypertrophy and collagen synthesis (i.e. prevent cardiac remodeling).

- Other tissue
- They ↓ apoptosis, ↓ cell hypertrophy, & ↓ collagen synthesis (i.e. they reduce degenerative changes caused by the action of Ang-II on AT1 receptors).

Therapeutic uses

Systemic hypertension:

✓ Hypertensive hypertension:
(Mention the mechanism)

* Normoreninemic hypertension:
because they are direct VDs.

Congestive heart failure (CHF):

- To ↓ afterload and preload through reduction of both systemic vascular resistance, venous return and aldosterone release (↓ Na and H₂O retention).
- To ↓ myocardial hypertrophy and dilatation (i.e. ↓ remodeling).

To prevent LV hypertrophy (remodeling) after acute MI through:

- ↓ arterial BP (↓ myocardial strain).
- ↓ myocyte cell hypertrophy, apoptosis, and collagen synthesis.



Normal



MI and necrosis



Ventricular remodeling

Cardiac remodelling means change in the size or shape of the heart due to dilatation, hypertrophy, or excessive formation of collagen scar.

After MI, myocyte cell necrosis triggers stimulation of the RAAS (Ang-II) triggers the formation of thick scar and myocyte hypertrophy leading to cardiac remodeling.

↑ collagen

+ myocyte hypertrophy

? Diabetic nephropathy & microalbuminuria:

- They ↓ renal changes complicating **diabetic nephropathy** (mesangial cell apoptosis, proliferation, and collagen synthesis), thus **reducing microalbuminuria** (provided that renal impairment is **not grave**).

Side effects: (better remembered by the mnemonic **CAPTORRIL**)

C : **Dry Cough** (the most common): inhibition of **ACE** leads to accumulation of **bradykinin** and **PGs**, which cause bronchial irritation and spasm.
Treatment: stop ACEIs. Cough will resolve after a few days.

A : **Angioedema** (edema of the face and throat): due to accumulation of **bradykinin** or due to immune reaction. It may be fatal.

P : Aggravation of **Proteinuria** in patients with significant renal failure.*

T : **Taste changes**: temporary loss of taste (**ageusia** and **dysgeusia**).

O : **Orthostatic (First dose) hypotension**: especially in sodium depleted (**hypovolemic**) patients.

Prevention: start by small at bedtime then increase gradually.

P : **Pregnancy**: **teratogenesis** (fetal **Pulmonary hypoplasia** and **growth retardation**)

R : **skin Rash**

I : **Increased K⁺ (hyperkalemia)** due to ↓ aldosterone release.

L : **Leukopenia** (**neutropenia**): especially in patients with **impaired renal function**. *



N.B. The **sulphydryl group (-SH)** present in captopril may be responsible for the immunological side effects e.g. **angioedema, taste changes, skin rash, leukopenia**.

Notes

SH → **ATRI** (immunological)
impaired renal → **leukopenia + proteinuria**
bradykinin → **Cough + Angioedema**
hypovolemic patients → **Orthostatic hypotension**

Contraindications

■ **Hypotension:** when systolic BP is less than 95 mm Hg.

■ **Severe renal failure or bilateral renal artery stenosis** ($\text{SCr} > 3 \text{ mg/dl}$). Why?

- In these conditions, the use of ACEIs is dangerous because they $\downarrow$ Ang-II $\rightarrow$ $\downarrow$ VC of the efferent arterioles $\rightarrow$ glomerular filtration pressure and $\downarrow$ GFR $\rightarrow$ aggravation of renal failure in both kidneys.
- Dangerous hyperkalemia may occur. $\uparrow K$
- Dangerous neutropenia may occur.

■ **Pregnancy and lactation:** they may cause fetal pulmonary hypoplasia and growth retardation.

■ **Hyperkalemia.**

■ **Neutropenia, thrombocytopenia, or severe anemia** (ACEIs may cause bone marrow depression).

■ **Immune problems:** whether due to autoimmune diseases or due to immunosuppressive drugs.

Precautions

- Initial dose should be small and at bedtime to avoid 1st dose hypotension.
- Frequent monitoring of kidney functions (SCr) and potassium levels one week after treatment and then every 3 months.
- Avoid use with K^+ sparing diuretics to avoid severe hyperkalemia.
- Remember all other contraindications...

Notes

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Angiotensin II receptor blockers (ARBs) (Losartan- Valsartan- Candesartan- Telmisartan)

- They selectively block AT₁ receptors.
- They have no effect on bradykinin metabolism. * use other inhibiting enzyme
- They have the potential for more complete inhibition of Ang-II action compared with ACE inhibitors because there are non-ACE enzymes (cathepsin and chymase) that can convert Ang-I into Ang-II.
- The adverse effects and contraindications are similar to those of ACE inhibitors but cough and angioedema are less common than with ACE inhibitors.

	ACE inhibitors	ARBs
Class	Angiotensin converting enzyme inhibitor (ACEI)	Angiotensin receptor blocker (ARB)
Mechanism	Inhibition of ACE leading to: ↓ VC effect of Ang-II ↑ VD bradykinins	Blocking of AT-1 receptors leading to ↓ VC effect of Ang-II <u>No bradykinin</u>
Efficacy in inhibition of RAAS	Less effective because other enzymes rather than ACE can convert Ang-I into Ang-II	More effective because it blocks AT-1 receptor, the final station responsible for Ang-II effects.
Cough and angioedema	Frequent due to ↑ <u>bradykinins</u>	Less frequent (they do not ↑ bradykinins)

Direct renin inhibitors: aliskiren

- Activation of angiotensinogen into Ang-I by renin is the rate limiting step in formation of RAAS.
- Aliskiren is a recently approved drug for treatment of hypertension. It inhibits renin activity and consequently the RAAS.
- The efficacy and side effects of aliskiren are comparable to ACEIs and ARBs.

Notes

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■ Calcium channel blockers (CCBs)

These are drugs that block voltage-gated Ca^{2+} channels.

N.B. Types of Ca^{2+} channels:

■ Voltage-dependent Ca^{2+} channels:

They open in response to cell membrane depolarization

L-type channels (Long lasting):

- It is the dominant type in cardiac and vascular sm ms.
- CCBs block this type of channels.

T-type channels (Transient).

N-type channels (Neuronal).

■ Receptor operated Ca^{2+} channels:

- These are Ca^{2+} channels linked to G-protein receptors.
- They open in response to $\uparrow$ intracellular IP_3 .
- Examples: Ca^{2+} channels coupled to α_1 receptors.

Classification of CCBs according to tissue selectivity

- CCB with mainly cardiac effects: verapamil, diltiazem.
- CCB with mainly vascular effects (dihydropyridines): nifedipine, amlodipine, nimodipine.
- CCB with main effect on other tissue: flunarizine, cinnarizine.

Pharmacological effects

CVS	Nifedipine	Diltiazem	Verapamil
Heart:			
- Negative inotropic effect:	-	++	$\downarrow$ +++
- A-V conduction delay:	-	++	$\downarrow$ +++
- HR:	$\uparrow$ (reflex)	$\downarrow$	$\downarrow \downarrow$
Blood vessels:			
- Coronary VD:	+++	++	++
- Peripheral VD:	+++	++	++
- Blood pressure:	$\downarrow \downarrow \downarrow$	$\downarrow$	$\downarrow$

Other effects

- They relax all smooth muscles (vascular, bronchial, GIT, uterine etc.).
- They $\downarrow$ Ca^{2+} -mediated cell necrosis and apoptosis.

Therapeutic uses

Cardio-selective CCBs (verapamil & diltiazem):

■ Ischemic heart disease (IHD):

- They $\downarrow\downarrow$ myocardial contractility and myocardial O_2 demand.
- They produce coronary VD and $\uparrow$ coronary blood flow.
- * They $\downarrow$ Ca^{2+} -mediated myocyte cell necrosis.

N.B. vasculoselective CCBs (dihydropyridines) e.g. nifedipine are also beneficial in IHD but they cause considerable peripheral VDs, so the dose should be adjusted to avoid hypotension and reflex tachycardia.

■ Cardiac arrhythmias: supraventricular tachycardia (SVT):

- SVT include atrial flutter, fibrillation, paroxysmal atrial tachycardia, etc.
- Verapamil $\downarrow$ SA node activity and A-V conduction, so it protects the ventricles from the rapid atrial rate (also β -blockers have the same effect).

N.B. Nifedipine is contraindicated as it causes hypotension and reflex tachycardia.

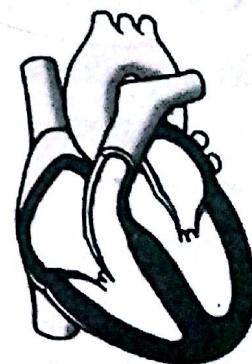
■ Hypertrophic obstructive cardiomyopathy (HOCM):

- In hypertrophic obstructive cardiomyopathy, the wall of the left ventricle and interventricular septum is much thickened leading to narrowing of the aortic outlet and obstruction of blood flow.
- Increasing contractility worsens the obstruction while decreasing contractility reduces resistance to blood flow through the aortic outlet and improve exercise tolerance.

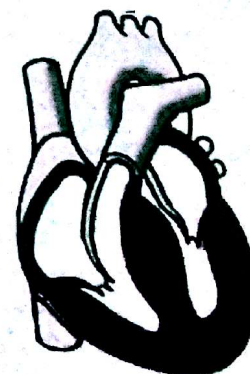
N.B. Nifedipine is contraindicated because it produces reflex tachycardia $\rightarrow$ worsening of the outflow obstruction:

■ Arterial hypertension:

- They $\downarrow$ myocardial contractility and COP.
- They cause peripheral VD due to $\downarrow$ Ca^{2+} influx in the vascular smooth ms.



Normal



Hypertrophic cardiomyopathy

VP → PVD
 → Cerebral Ischemia

uterus relaxation

Vasculo-selective CCBs (Nifedipine and amlodipine):

- Systemic hypertension.
- Peripheral vascular disease (e.g. Raynaud's disease and intermittent claudication) to improve peripheral microcirculation.
- * Nifedipine is sometimes used to relax the uterus and delay preterm labor.
- * Nimodipine has high affinity for cerebral BV. It is used for prevention of cerebral vasospasm and ischemia complicating subarachnoid hemorrhage.

Adverse effects

Verapamil & diltiazem:

- Bradycardia and heart block
- Worsening of CHF (due to their -ve inotropic effect).
- * Constipation due to ↓ GIT motility.

Nifedipine:

- Hypotension and reflex tachycardia.
- Gingival (gum) hyperplasia.
- Salt & water retention (ankle edema; more common than with verapamil due to significant VD and hypotension).

How to treat ankle edema if occurred with CCBs?

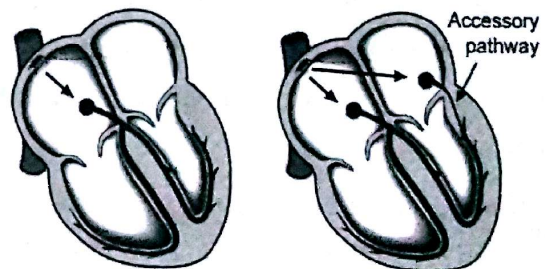
- Minimize sodium intake.
- Avoid prolonged standing.
- Mild diuretics.

Contraindications & precautions

Verapamil & diltiazem:

- ✓ Congestive heart failure.
- ✓ Bradycardia, and heart block.
- Wolff-Parkinson-White syndrome:

In WPW syndrome, there is accessory conducting pathway between atria and ventricles other than the normal A-V system. There is ventricular arrhythmia because one ventricle is excited before the other.



Verapamil and diltiazem will ↓ conduction in the normal pathway but they ↑ conduction in the abnormal pathway → worsening of arrhythmia.

- ✓ Verapamil should not be combined with digitalis or β-blockers as it may cause A-V block due to augmented bradycardia (nifedipine is the drug of choice to be used with β-blockers because it doesn't cause bradycardia).

Nifedipine:

- Hypotension.
- Hypertrophic obstructive cardiomyopathy (HOCM) Why?
- Unstable angina (risk of reflex tachycardia and coronary steal).
- Supraventricular tachycardia (SVT) Why?

Notes

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Vasodilators

Arterio-dilators: Nifedipine – Hydralazine – Minoxidil – Diazoxide.

- They dilate arteries and $\downarrow\downarrow$ BP ($\rightarrow \downarrow$ afterload)
- They are used in severe systemic hypertension.

Venodilators: Nitrates.*

- They dilate mainly veins $\rightarrow \downarrow$ venous return ($\rightarrow \downarrow$ preload)
- They are used in acute pulmonary edema.

Mixed dilators: Sodium nitroprusside – Prazosin – ACEIs – Trimetaphan.

- They $\downarrow$ preload & afterload so they are used in CHF.

General considerations

- Vasodilators relax vascular smooth ms and $\downarrow$ peripheral resistance.
- They usually cause reflex sympathetic stimulation (e.g. reflex tachycardia) so they can be combined with beta-blockers.
- They usually cause salt and water retention (due to $\uparrow$ aldosterone release) so they should be combined with diuretics.
- The use of vasodilators is declining as a result of newer modalities, such as ACEIs and CCBs, which are more effective with fewer adverse effects.

Hydralazine

- It is a direct arteriolodilator by unclear mechanism.
- It is used in severe hypertension and hypertension in pregnancy (2nd choice after α -methyl dopa).
- It is usually combined with diuretics to counteract salt and water retention, and β -blockers to counteract reflex tachycardia.
- It may cause systemic lupus erythematosus (SLE)-like syndrome in slow acetylators.



SLE-like rash caused by hydralazine

Minoxidil

Orally to chronic hypertension
Topically to hair loss

- It is a direct arteriolodilator by opening K^+ channels $\rightarrow$ hyperpolarization $\rightarrow$ relaxation of the vascular smooth ms.
- It is given orally for chronic hypertension but its use as antihypertensive is declining; however, it should be combined with diuretics and β -blockers.
- It was found to stimulate hair growth (hypertrichosis) (by unclear mechanism), so it is now used topically to prevent hair loss in both males and females.

Diazoxide

K⁺ emergency

hypertrichosis

- Structurally related to thiazides but it is not diuretic.
- It is a direct arteriolodilator by opening K^+ channels $\rightarrow$ hyperpolarization $\rightarrow$ relaxation of the vascular smooth ms.
- It is given parenterally in hypertensive emergencies but its use is declining.

Sodium nitroprusside

NO

- It liberates nitric oxide (NO) $\rightarrow$ $\uparrow$ cGMP $\rightarrow$ dilatation of both arteries and veins $\rightarrow$ $\downarrow$ both preload and afterload.
- It is given by i.v. infusion in hypertensive emergencies and acute heart failure because it has rapid action.
- It can be converted to cyanide and thiocyanate. The accumulation of cyanide and risk of toxicity are minimized by concomitant administration of sodium thiosulfate (see angina) or hydroxocobalamin (vitamin B12).

thiocyanide

thiocyanide

thiocyanate

- Sodium nitroprusside in aqueous solution is sensitive to light and must be made up fresh before each administration and covered with opaque foil.

Fenoldopam

- It stimulates peripheral dopamine (D1) receptors in renal and mesenteric arteries, leading to VD and decrease peripheral resistance.
- It is used parenterally as a rapid-acting vasodilator to treat emergency hypertension in hospitalized patients.

Endothelin-1 receptor antagonists

a → selective on A
b → non-n

- Endothelin-1 is (21 amino acid) peptide. It is the predominant endothelin secreted by the vascular endothelium. It is elevated in patients with pulmonary hypertension.
- It acts on two types of receptors, ET_A and ET_B. ET_A receptors is the main subtype in smooth muscles and mediates VC and vascular smooth ms hypertrophy. diuresis
- Bosentan is orally active nonselective blocker of ET_A and ET_B receptors, while ambrisentan is a selective ET_A blocker.
- Both drugs are approved for treatment of pulmonary hypertension. *

Specialized vasodilators

Drugs used for erectile dysfunction: Sildenafil, tadalafil

- These drugs inhibit phosphodiesterase type 5 the enzyme responsible for breakdown of cGMP in erectile tissue and the lung → ↑ cGMP → VD of the corpus cavernosum.
- They are very effective for treatment of erectile dysfunction in men. → psycho
- Sildenafil is also approved for treatment of pulmonary hypertension.
- These drugs are contraindicated in patients taking nitrates for treatment of angina because nitrates also act by ↑ cGMP → severe VD, hypotension, and reflex tachycardia → aggravation of angina and development of arrhythmia.

Notes

phosphodiesterase 3 → heart BV
~
5 → eye + other BV + penis BV
4 → CNS

Practical guidelines for management of systemic hypertension

Systemic hypertension is persistent elevation of BP above 140/90.

Classification of hypertension:

- According to etiology: primary (= essential, 90%) or secondary.
- According to type: systolic, diastolic, or mixed.
- According to degree: see table.

Classification of blood pressure levels of the British Hypertension Society

Category	Systolic BP (mmHg)		Diastolic BP (mmHg)
Blood pressure			
Optimal	<120	and	<80
Normal	120-129	and/or	<80-84
High normal	130-139	and/or	85-89
Hypertension			
Grade 1 (mild)	140-159	and/or	90-99
Grade 2 (moderate)	160-179	and/or	100-109
Grade 3 (severe)	≥180	and/or	≥110
Isolated <u>systolic</u> hypertension			
Grade 1	140-149		<90
Grade 2	>160		<90

N.B. If systolic and diastolic BP fall into different categories, the higher value should be taken for classification.

Therapy of hypertension

- For most patients, the goal of therapy is to maintain BP < 140/90 mm Hg.
- In patients with diabetes or chronic kidney disease, BP should be < 130/80 mm Hg.

Non-drug therapy = life style modification:

- Dietary sodium restriction and potassium and magnesium supplementation.
- Stop smoking and avoid stress.
- Weight reduction alone can correct hypertension in 75% of obese patients.

- Daily physical exercise (30 -60 min/day at least).
- Control of risk factors e.g. diabetes mellitus, hyperlipidemia, and obesity.
- Avoid drugs that $\uparrow$ BP e.g.: sympathomimetics, sodium-containing drugs, oral contraceptives, corticosteroids.

N.B. Patients failing to normalize BP after 2 weeks of non-pharmacological therapy should be considered for drug treatment.

Drug therapy (antihypertensive drugs):

First choice groups (commonly used drugs)	Second choice groups (used in special cases):
▪ <u>ngiotensin-converting enzyme inhibitors (ACEIs).</u> ▪ <u>eta-blockers.</u> ▪ <u>alcium channel blockers.</u> ▪ <u>iuretics.</u>	▪ <u>α_1- blockers:</u> prazosin and doxazosin. ▪ <u>Combined α and β-blockers:</u> labetalol. ▪ <u>Adrenergic neuron blockers:</u> α-methyldopa and reserpine. ▪ <u>Direct vasodilators:</u> hydralazine and diazoxide. ▪ <u>Central α_2 stimulants:</u> clonidine. ▪ <u>Endothelin receptor blockers:</u> Bosentan. ▪ <u>Dopamine receptor agonists:</u> fenoldopam.

Choice of the antihypertensive drugs:

Clinical condition	Best choice
Starting therapy for <u>non-complicated essential hypertension</u>	<u>Thiazides</u> If not adequate, add a <u>beta-blocker</u> or <u>ACE inhibitor</u>
Hypertension in <u>pregnancy</u>	<u>Alpha-methyldopa</u> If not adequate, use <u>hydralazine</u>
Hypertension in a <u>diabetic patient with diabetic nephropathy (proteinuria)</u>	<u>ACE inhibitors</u> $\rightarrow$ improve glu. tolerance
Hypertension with <u>chronic kidney disease</u>	<u>CCBs, ACE inhibitors</u>
Hypertension with <u>CHF</u>	<u>ACE inhibitors</u> and <u>diuretics</u>

Anything ex B. bla-

Hypertension with bronchial asthma

CCBs

Anything except
B blockers

Hypertension with angina

CCBs and beta-blockers

Hypertension with thyrotoxicosis, increased sympathetic activity, or young patient with high plasma renin

Beta-blockers

Hypertension with benign prostatic hypertrophy

α 1 blockers

Pulmonary hypertension

Endothelin receptor antagonists

Sildenafil

Management of hypertensive emergencies:

Hypertensive emergencies are clinical situations associated with one or more of the following:

- BP is greater than 180/120 mmHg
- Target organ damage e.g. cerebral stroke, encephalopathy, heart failure, aortic dissection, edema of the optic disc (papilledema).

Hypertensive encephalopathy

Is a clinical presentation consists of severe headache, mental confusion, blurred vision, and focal neurologic signs. If untreated it may progress over a period of 12–48 hours to convulsions, coma, and even death.

Management

- Hospitalization and start parenteral antihypertensive medications to lower BP rapidly (within a few hours not minutes).
- Chronic hypertension is associated with autoregulatory changes in cerebral blood flow, so rapid normalization of BP may lead to cerebral hypoperfusion and brain injury.
- The initial target in the first 1–2 hrs is to lower BP by no more than 25%, maintaining diastolic BP at no less than 100 mmHg.
- Drugs commonly used are:
 - Sublingual: nifedipine or captopril.
 - Parenteral: sodium nitroprusside, fenoldopam, nitroglycerine, diazoxide, furosemide, labetalol.

Part 2: Ischemic Heart Disease and Antianginal Drugs

Ischemic heart disease (IHD) includes:

Chronic stable angina (Classic; angina of effort):

- It is due to atheromatous narrowing of the coronary artery.
- Pain is induced by effort and lasts for minutes disappears with rest.

Acute coronary syndromes: (preinfarction)

- **Unstable angina:** It is due to rupture of atheromatous plaque and formation of thrombus. The patient experiences acceleration in the frequency or severity of chest pain, or new-onset angina pain.

- **Myocardial infarction:** An intraluminal thrombus completely occludes the epicardial coronary artery at the site of plaque rupture leading to irreversible coagulative necrosis.

Afterload: it is the resistance that the ventricles must overcome to eject blood during systole. It is mainly determined by the resistance of the arterial side.

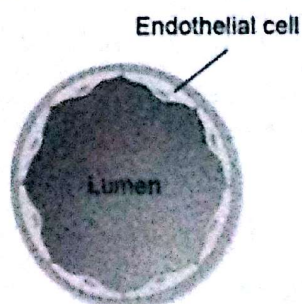
Preload: the stress (stretch) of the ventricular wall caused by venous filling just before contraction (also known as end-diastolic pressure). It is mainly determined by the amount of venous return (VR).

N.B. veins are capacitance vessels; venodilatation leads to decrease VR and preload.

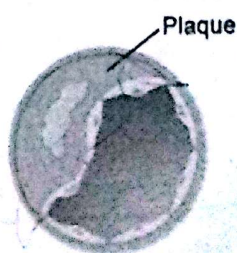
Prinzmetal's angina (Variant angina; angina of rest; α_1 -mediated angina):

The coronary artery undergoes severe spasm due to overactivity of α_1 receptors. The patient develops pain at rest.

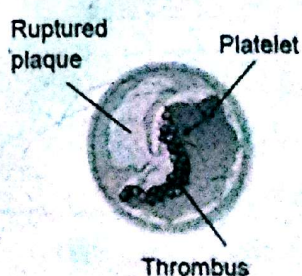
A Normal



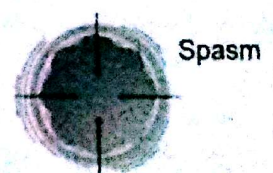
B Stable angina



C Unstable angina



D Variant angina



Chronic stable angina

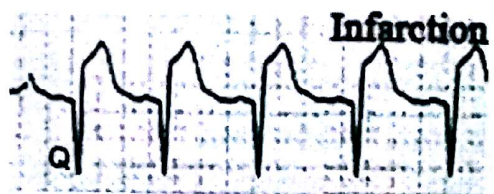
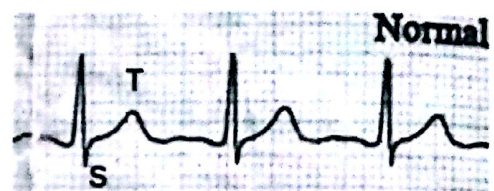
Definition: retrosternal pain (due to atherosclerosis ischemia of the myocardium as a result of imbalance between heart work (O_2 demand) and coronary blood flow (O_2 supply)).

Clinical picture: Pain is the cardinal symptom:

- Site and radiation: retrosternal, radiating to the left shoulder and the left arm.
- Character: any character (usually sense of chest tightness).
- Provocative factors: effort, cold weather, stress, etc.
- Duration: usually not more than 5 min. If prolonged → suspect acute MI.

Diagnosis:

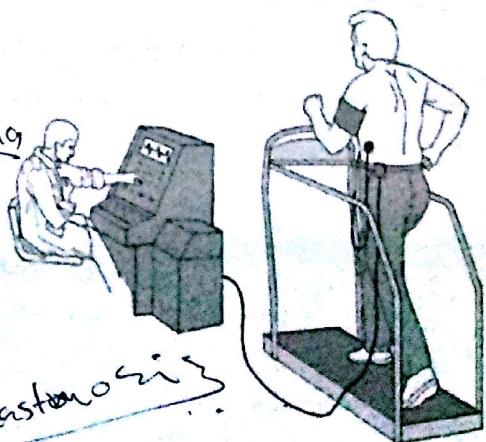
- **ECG:**
 - In between the attacks: the ECG may be completely normal (so we can't depend on ECG only for diagnosis).
 - During ischemia: there is ST segment depression and T-wave inversion.
 - In myocardial infarction: there is deep Q-wave.
- **Stress test:** recording ECG under controlled physical effort to record ST segment depression and T-wave inversion.
- **Continuous 24-hour ECG recording** (Holter monitoring).
- **Coronary angiography.** *أخذ صورة*



Management of stable angina

Non-drug therapy = life style modification:

- Dietary sodium & fat restriction.
- Avoid stress and stop smoking & coffee.
- Weight reduction.
- Mild physical exercise: to improve collateral circulation of the heart.
- Control of risk factors: e.g. DM, hyperlipidemia, and obesity.
- Avoid vasoconstrictor drugs e.g. sympathomimetics, migraine medications.



■ Drug therapy (Antianginal drugs):

■ Drugs given during the acute attack:

- Short-acting nitrates.
- Sedatives to relieve anxiety and sympathetic stimulation.

■ Drugs given in-between the attacks (prophylaxis):

- Long-acting nitrates.
- Beta-blockers
- CCBs.
- pFOX inhibitors: trimetazidine
- Newer antianginal drugs: ranolazine
- Antiplatelet drugs: e.g. aspirin, clopidogrel, etc.

■ Surgical treatment (myocardial revascularization).

■ Organic nitrates and nitrites

Classification

	Dose	Onset	Duration
Short-acting nitrates:			
Amyl nitrite (inhalation)	0.3 ml	1-2 min	5-10 min
Nitroglycerine (SL)	0.5 mg	1-5 min	10-20 min
Isosorbide dinitrate (SL)	5 mg	3-5 min	60 min
i.v. nitroglycerin (Tridil)	5 µg/min		
Intermediate-acting nitrates:			
Isosorbide dinitrate (Oral)	10 mg	15 min	3-6 hrs
Oral SR	40 mg	30 min	6-10 hrs
Long-acting nitrates:			
Isosorbide mononitrate (Oral)	20 mg	30 min	6-8 hrs
Oral SR	60 mg	30 min	6-10 hrs
Transdermal patches		30 min	12-18 hrs

Notes

rectal nitroglycerine → angina during rest (at night)

Pharmacokinetics

Absorption: nitrates are rapidly absorbed from all sites of administration.

Metabolism: in the liver

- If given oral → extensive first-pass metabolism (oral bioavailability < 10%)
- If given sublingual → no first-pass metabolism → high bioavailability.

Mononitrate: has no hepatic metabolism → long duration of action.

Excretion: via the kidney.

Mechanism of action

- Nitrates cause formation of the free radical nitric oxide (NO) which is identical to the endothelial derived relaxing factor (EDRF) → ↑ cGMP → VD (more on veins than arteries).
- They also ↑ formation of PGE₂ and PGI₂ → VD.

Pharmacological effects

CVS:

Blood vessels:

- VD of the venous (and to lesser extent the arterial) side leading to ↓ preload and ↓ afterload → ↓ cardiac work.
- VD of coronary arteries leading to increased coronary blood flow.
- VD of arteries in the face and neck leading to flushing of the face.
- VD of meningeal arteries leading to throbbing headache.

Heart: Reflex tachycardia (in high dose) try to ↓ BP.

BP: High doses cause ↓↓ in both systolic and diastolic BP.

Smooth ms: Relaxation of bronchial, GIT, uterine, and biliary smooth ms.

* Respiration: Reflex tachypnea (↑ resp rate) due to hypotension.

* Blood: Methemoglobinemia in high doses due to oxidation of Hb into met-Hb.

Therapeutic uses

■ Angina pectoris

→ angina
→ MI
→ AHF
→ cyanide poisoning

Nitrates are used for treatment of all types of angina both for relieving the acute attack and for prophylaxis. The mechanism is due to:

- Nitrates cause formation of the free radical nitric oxide (NO) which is identical to the endothelial derived relaxing factor (EDRF) → ↑ cGMP → VD (more on veins).
- They also ↑ formation of PGE₂ and PGI₂ → VD.

These effects will lead to:

▪ Decrease cardiac work & myocardial O₂ demand through:

- Venodilatation → ↓ venous return (preload = ↓ end-diastolic pressure).
- Arteriolodilatation → ↓ peripheral resistance (afterload).

▪ Enhancement of coronary blood flow (perfusion) through:

- Coronary VD. *healthy only so*
- Redistribution of blood from large epicardial vessels to ischemic subendo-cardial vessels. → by *constansis between healthy & ischemic*

▪ Myocardial infarction: to ↓ ^{size} the area of myocardial damage.

▪ Acute heart failure: to ↓ preload and afterload.

▪ Treatment of cyanide poisoning

Side effects

- Hypotension and reflex tachycardia: may aggravate angina.
- Throbbing headache: due to VD of meningeal arteries.
- Flushing of the face.

① Tolerance to its effect: due to:

- Oxidation of sulfhydryl (-SH) group by chronic use of nitrates leading to depletion of SH-containing enzymes necessary for formation of NO → ↓ formation of NO and cGMP → ↓ VD effect.
- Reflex sympathetic stimulation (due to hypotension), leading to VC and sodium retention. *compensatory mechanism*

► Prevention of nitrate tolerance: make a daily nitrate-free interval (10-12 h) to give chance for SH-containing enzymes to regenerate. During this period, give another anti-anginal drug e.g. beta-blocker or CCBs.

② Methemoglobinemia: rare and require high doses. *200 mg*

Treatment of cyanide poisoning

Principle: cyanide has high affinity for metHb more than normal Hb.

- Sodium nitrite (300 mg i.v.) is given to convert part of Hb to metHb to attract cyanide ions and form cyan-metHb.
- Sodium thiosulphate (25 gm i.v.) is given to convert cyan-metHb to (thiocyanate) (non-toxic) → renal excretion.

Notes

CUA Pharmacol Dept.
Faculty of Medicine
Mansoura University

Precautions during nitrate therapy

- Use the **smallest effective dose** to avoid hypotension and reflex tachycardia.
- The patient should **consult his doctor** if anginal pain does not improve after taking 3 SL tablets of NG during 15 min (the pain may be due to MI).
- Nitroglycerine tablets should not be put in **direct sunlight** (light sensitive) or with **cotton** (to avoid formation of the explosive **nitrocellulose**).
- The **expiry date** should be checked (active tablets have **burning taste**).
- **Avoid sudden withdrawal** because it may lead to **acute MI**.

Beta-blockers

Mechanism in angina

- They ↓ contractility, HR, and systolic BP → ↓ myocardial work and O₂ demand.
- They ↑ diastolic (coronary) filling time.
- Cause redistribution of blood from normal to ischemic (subendocardial) regions
- Cytoprotective effect: they produce metabolic switch from myocardial fat utilization to carbohydrates utilization (i.e. improves myocardial metabolism).

Combination of BBs and nitrates ↑ their efficiency & ↓ their side effects:

	β-blockers	Nitrates	Combination
- HR	↓	↑ (Reflex)	↓ or no effect
- Contractility	↓	↑ (Reflex)	↓ or no effect
- Diastolic filling time	↑	↓	↑ or no effect
- Blood pressure	↓	↓	↓↓

N.B. Beta-blockers are **contraindicated** in **Prinzmetal's (variant) angina** because they **block the β₂-mediated coronary dilatation** leaving the α₁ receptors unopposed → ↑ coronary spasm.

→ we use **CCBs** *diltiazem*

Calcium channel blockers (CCBs): See hypertension.

Notes

Combination the same as B + Nite.

Ebrahim Said behairy

pFOX inhibitors (metabolic modifiers): e.g. Trimetazidine

Mechanism

- They are termed pFOX inhibitors because they partially inhibit fatty acid oxidation in the myocardium.

This "metabolic switch" from fats to carbohydrate utilization requires less O_2 consumption.

- By inhibition of fatty acid oxidation, they $\downarrow$ intracellular lactic acidosis leading to $\downarrow$ intracellular Ca^{2+} & Na^+ accumulation and ion disturbance, so they prevent cell necrosis and preserve contractile function.

- Trimetazidine also $\downarrow$ membrane damage caused by oxygen free radicals.

antioxidant effect

Newer antianginal drugs: Ranolazine

- Ranolazine is a new antianginal drug.
- It $\downarrow$ intracellular Ca^{2+} indirectly by reducing the late sodium current that facilitates Ca^{2+} entry into myocardial cells. The reduction in intracellular Ca^{2+} concentration reduces cardiac contractility and work.
- It also produces metabolic switch like trimetazidine

Antiplatelet drugs: e.g. aspirin and clopidogrel (See blood).

Choice of antianginal drugs in patients with another disease:

Angina with....	Most preferred	Least preferred
Bronchial asthma	Nitrates, CCBs	Beta-blockers
Heart failure	Nitrates, Nifedipine	Beta-blockers, Verapamil
Hypertension	Beta-blockers, CCBs	Nitrates
Diabetes mellitus	Nitrates, Nifedipine	Beta-blockers, Verapamil

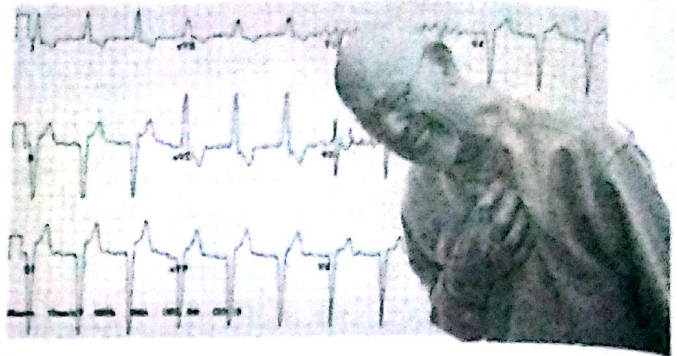
Notes: interfere with insulin Sec. $\rightarrow$ by blocking Ca channels

* in inferior MI Morphine is contraindicated because it has a broad Cushing effect also pentazocin and butorphanol → ↑ vascular resistance but we can use meperidine → has atropine like action

Management of acute myocardial infarction (AMI)

(The patient should be hospitalized) and MONA (Morphine, Oxygen, Nitroglycerine, Aspirin) risk

- **Hospitalization (coronary care unit):** to control vital signs (respiration, HR, BP, pulse, etc.) and continuous monitoring of ECG.



- **Morphine sulfate (5 mg i.v.):**
 - To produce analgesia.
 - To ↓ stress of the patient → ↓ sympathetic discharge and heart work.
 - Morphine causes venodilatation → ↓ venous return and ↓ cardiac work.

- **Oxygen:** by nasal cannula or mask.

- **Nitroglycerine and beta-blockers:** to limit the infarct size.

- **Anticoagulant drugs:** heparin 10,000 IU i.v. then 5000 IU/8h s.c. especially when the patient is obese or if there is history of previous MI.

- **Thrombolytic (fibrinolytic) therapy:** streptokinase, urokinase, pro-urokinase as early as possible (see blood).

- **Sedatives:** diazepam 5 mg i.v.

Treatment of Complications:

- **Cardiogenic shock** → give dobutamine i.v.
- **Arrhythmia** → give lidocaine i.v.

- **Treatment of risk factors:** stop smoking, control hypertension, obesity, etc.

Morphine and AMI

- Morphine is usually given s.c. but in AMI it is given 5 mg i.v.
- Morphine is contraindicated in cases of MI involving the inferior wall of the heart (inferior MI) because in this case, the patient has bradycardia and morphine causes vagal stimulation → aggravation of bradycardia.
- What another opioid analgesic could be used in inferior MI? Meperidine because it has atropine-like action → counteract bradycardia.
- What other opioid analgesics are contraindicated in AMI? Pentazocin and butorphanol because they ↑ pulmonary and systemic vascular resistance → more strain on the heart (see CNS).

Part 3: Drug Therapy of Congestive Heart Failure (CHF)

Definition of HF: Inability of the heart to pump sufficient blood to tissues due to myocyte dysfunction or death.

Classification, clinical picture, and therapeutic aim:

■ According to anatomy:

Left-sided heart failure:

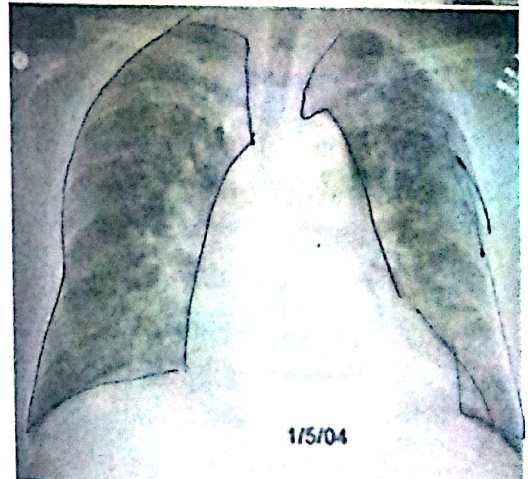
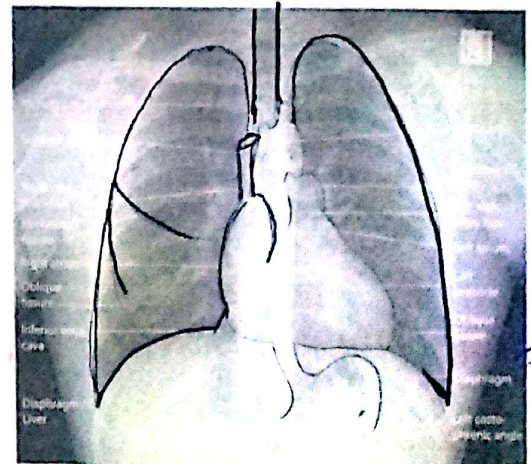
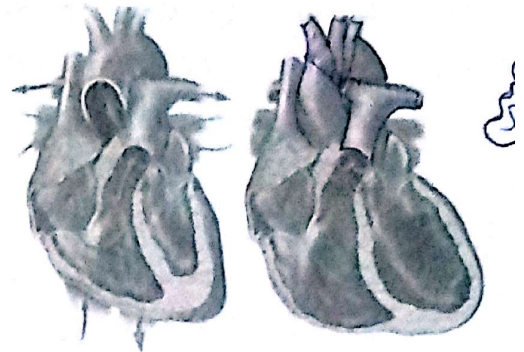
- Usually due to systemic hypertension.
- The cardinal manifestations are those of pulmonary congestion e.g. tachypnea, dyspnea (difficulty in breathing), orthopnea (dyspnea on lying back), paroxysmal nocturnal dyspnea, and cough with expectorations.
- **Signs:** LV hypertrophy, ejection fraction <60%, bilateral basal lung crepitations, and gallop (3rd heart sound).
- The aim of therapy is to ↓ afterload.

Right-sided heart failure:

- Usually due to pulmonary hypertension or lung disease.
- The cardinal manifestations are those of systemic congestion e.g. congested neck veins, congested liver, bilateral leg edema, right ventricular hypertrophy, etc.
- The aim of therapy is to ↓ preload.

Total heart failure (congestive heart failure "CHF"):

- Combination between the two.
- The aim of therapy is to ↓ both afterload and preload.



■ According to state of the COP:

High COP failure:

- Occurs in cases of hyperdynamic circulation (e.g. thyrotoxicosis, severe anemia, etc.).
- The heart increases its work to match the high tissue need, but finally fails.
- The aim of therapy in this condition is to RELAX the heart by beta-blockers NOT to increase its work by +ve inotropic drugs.

Low COP failure:

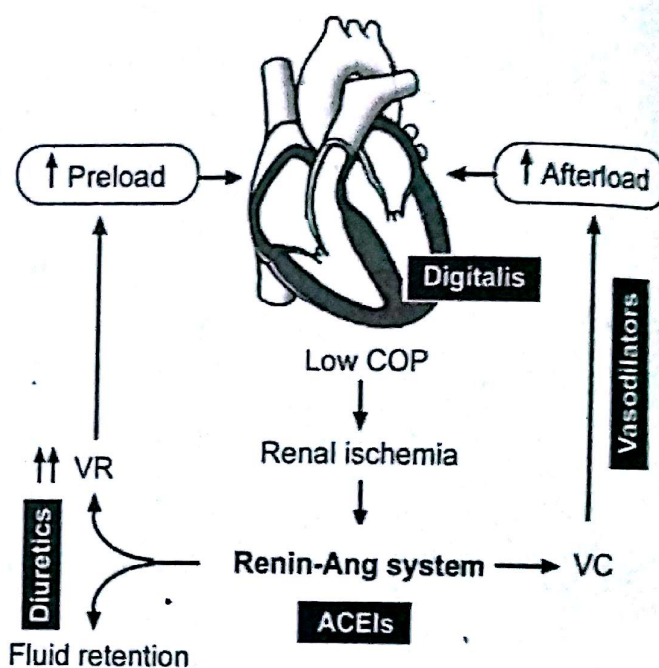
- Occurs when the heart is unable to pump all the blood filling the ventricles.
- The aim of therapy in this condition is to STRENGTHEN the cardiac ms, by giving +ve inotropic drugs NOT to relax the heart by beta-blockers or CCBs.

Pathophysiology of heart failure

Low COP → renal ischemia → ++ of RAAS → VC (Ang-II) and fluid retention (aldosterone) → ↑ afterload and preload → more HF and edema (vicious circle).

Investigations

- ECG: left ventricular hypertrophy.
- Cardiac echo.
- Chest X-ray: cardiomegally and signs of pulmonary congestion.



■ Pharmacotherapy of heart failure

■ Non-drug therapy = life style modification:

- * Rest. ✓
- Dietary sodium (salt) and fat restriction. ✓
- Avoid stress, smoking and alcohol. ✓
- Weight reduction. ✓
- Control of risk factors e.g. surgical correction of valvular diseases and treatment of hyperthyroidism, hypertension, etc.
- Avoid drugs that ↑ BP: e.g. sympathomimetics, sodium containing drugs, etc.

Drug therapy:

Positive inotropic drugs:

- Cardiac glycosides (Digitalis).
- Dopamine & dobutamine (used for short term only).
- Phosphodiesterase inhibitors: inamrinone & milrinone.

Diuretics

ACEIs

Vasodilators

Other drugs: e.g. beta-blockers.

↓ pre load

↓ pre load

↓ both

↓ after load

↑ Symp

↑ Pheochromocytoma

↑ thyrotoxicosis

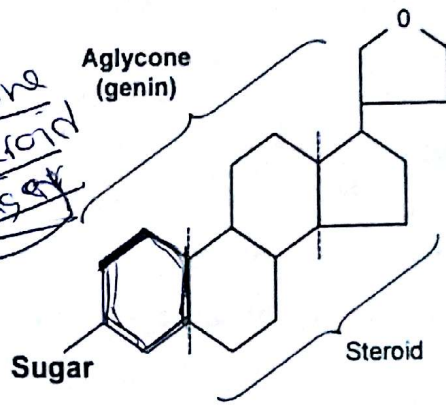
Cardiac glycosides:

Digoxin, Digitoxin, Ouabain

Source and chemistry

- Natural plant derivatives (Foxglove plant).
- Cardiac glycosides contain a lactone ring and a steroid (aglycone) moiety attached to sugar molecules.

Digoxin is the most widely used.



Pharmacokinetics of digoxin

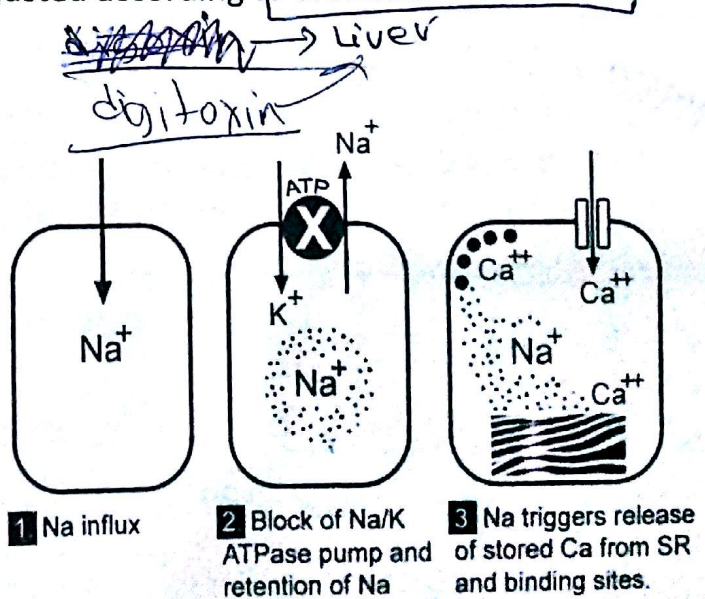
- Digoxin distributes to most body tissues and accumulates in cardiac tissue. The concentration of the drug in the heart is twice that in skeletal muscle and at least 15 times that in plasma.

Elimination is renal. Dose should be adjusted according to creatinine clearance.

Mechanism of action

Positive inotropic effect:

Digitalis ↑ cardiac contractility by increasing free intracellular Ca^{2+} through inhibition of membrane-bound Na^+/K^+ ATPase enzyme. This results in inhibition of Na^+/K^+ pump with subsequent accumulation of intracellular Na^+ and Ca^{2+} via:



- ① - Increase Ca^{2+} release from the sarcoplasmic reticulum.
- ② - Displacement of intracellular Ca^{2+} from its binding sites.
- ③ - Increased Intracellular sodium reduces Ca^{2+} expulsion from the cell by the $\text{Na}^+/\text{Ca}^{2+}$ exchanger.

Autonomic effects:

- ↑ vagal activity: By direct and indirect mechanisms.
- ↓ sympathetic activity due to relieve of hypoxia & improved tissue oxygenation.

Pharmacological effects

- ↑ **Contractility** and **COP**: due to +ve inotropic effect. This leads to:
 - Improvement of **RBF** → **diuresis** and ↓ **RAAS** (i.e. ↓ fluid retention).
 - Relief of **lung congestion**.

- ↓ **HR**: (**Bradycardia**) due to:
 - ↑ vagal tone and ↓ sympathetic activity on the heart.
 - * - Direct inhibition of the **A-V conducting system**.

Conduction velocity:

- **Atrial conduction**: ↑ due to vagal stimulation.
- **A-V conduction**: ↓↓ by direct and vagal effects.

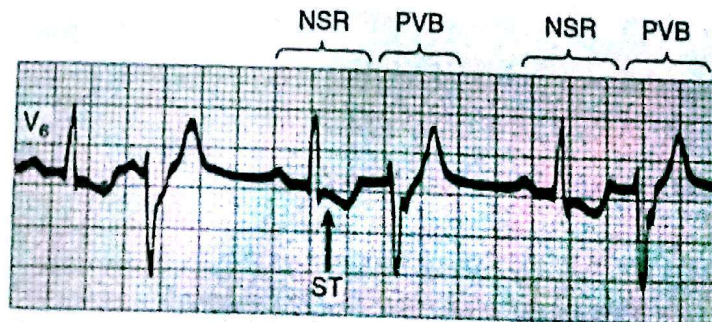
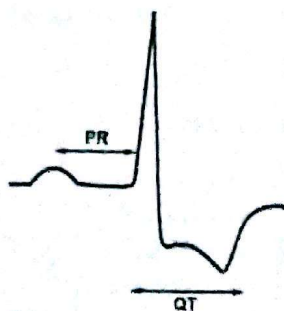
- ↑ **Excitability and automaticity** leading to **ectopic foci** activation and **arrhythmia** of any type (usually bigeminy, trigeminy, etc.).

ECG changes:

- Prolonged **PR interval**.
- Short **QT interval**

ST segment depression & T-wave inversion.

- Normalization of arterial and venous pressures due to improved hemodynamics.



ECG record showing digitalis-induced bigeminy. The complexes marked NSR are normal sinus rhythm beats; an inverted T wave and depressed ST segment are present. The complexes marked PVB are premature ventricular beats

Therapeutic indications

- The major indication is chronic CHF associated with atrial fibrillation.
- Supraventricular arrhythmias:
 - Atrial flutter: (the atria beat regularly at 200-400 bpm)
 - Atrial fibrillation: (the atria beat irregularly at 400-600 bpm)
 - Paroxysmal atrial tachycardia.

Mechanism:

- $\downarrow$ A-V conduction and protects the ventricles from the accelerated atria.
- Improvement of atrial function (due to improved hypoxia).

N.B. The use of digitalis in HF is now shrinking after the introduction of diuretics and vasodilators, even in cases of supraventricular tachycardias **verapamil** is preferred.

Contraindications

Absolute contraindications:

- **Heart block**, because digitalis worsens A-V conduction by direct and vagal effects.
- **Hypertrophic obstructive cardiomyopathy (HOCM)**: because increasing cardiac contractility will $\uparrow$ the outflow tract resistance and accelerates heart failure (see before).
- **Wolff-Parkinson-White (WPW) syndrome**, although digitalis (and verapamil) $\downarrow$ conduction in the normal pathway, they can $\uparrow$ conduction in the abnormal pathway leading to $\uparrow$ arrhythmia (see before).
- **Paroxysmal ventricular tachycardia**: because digitalis $\uparrow$ excitability and automaticity
 any type of ven. arrhythmia

Relative contraindications:

- **Bradycardia** or sick sinus syndrome.... Severe bradycardia may occur.
- **Hypersensitive carotid sinus**..... Severe bradycardia may occur.
- With **beta-blockers** or **verapamil**... Severe bradycardia may occur.
- **Systemic hypertension** (hypertensive HF): digitalis will $\uparrow$ the strain of the L. ventricle (you must correct hypertension first by giving VD's or diuretics).

③ → obstructive cardiovascular diseases
 ② → strain
 ② - **Pulmonary hypertension** due to **chronic lung disease**: digitalis will ↑ the strain of the R. ventricle (you must correct pulmonary hypertension first by giving VDs).

- **Cardiac diseases:**

- **Acute MI**: digitalis ↑ the infarct size and aggravates arrhythmia.
- **Cardiomyopathy**: digitalis is useless.

Renal or hepatic diseases: digoxin must be avoided in renal patients while digoxin must be avoided in hepatic patients.

In patients likely to require **cardioversion**: because digitalis may lead to fatal arrhythmia if given with cardioversion. → artificially pass water
application electrical current
to the chest wall

Drug interactions

Drug	Mechanism/effect
Antacids <u>Kaolin</u>	Bind digoxin in the gut and <u>decrease bioavailability</u>
Cholestyramine	(<u>absorption</u>)
Metoclopramide	Increase gut motility leads to <u>decrease digoxin absorption</u> .
Atropine	Decrease gut motility leads to <u>increase digoxin absorption</u>
Quinidine	Decrease renal clearance of digoxin and <u>displace digoxin from plasma proteins</u> . Serum digoxin is increased.
Loop diuretics and thiazides	Thiazides or loop diuretics may cause <u>hypokalemia</u> and <u>hypomagnesemia</u> and increase the risk of <u>digitalis toxicity</u>

Dosage and administration

Initial digitalization:

1-2 mg/m²

Slow (cumulative) method:

- It is done by giving one tablet 0.25 mg/day (5 days/week) from the start.
- The steady state plasma conc (C_{ps}) will be achieved after **5 half-lives** (i.e. after one week for digoxin).
- It is the safest method for digitalis administration.

Emergency

Rapid (loading) method:

- It is done in emergency conditions to achieve rapid C_{ps}.
- 2 tablets (0.5 mg) twice daily for 2 days (2x2x2).

■ **Maintenance dose**: one tablet (0.25 mg)/day, 5 days/week.

slowly

Assessment of response to digitalis

- Relief of dyspnea and orthopnea.
- Relief of tachycardia and tachypnea.
- Relief of edema, lung congestion, and fatigue.
- Increase urine volume. → ↑RBF
- Improvement of physical performance. relief fatigue

N.B.

- The optimum therapeutic plasma level is 1-2 ng/ml.
- Arrhythmia occurs when the level exceeds 2 ng/ml.

Precautions during digitalis therapy avoid toxicity

- Never give digitalis i.v. before being sure that the patient has not received digitalis during the last 14 days to avoid digitalis toxicity.
- Continuous monitoring of plasma K^+ level. → hypokalemia → digitalis toxicity
- Mention all the relative contraindications.

Digitalis toxicity

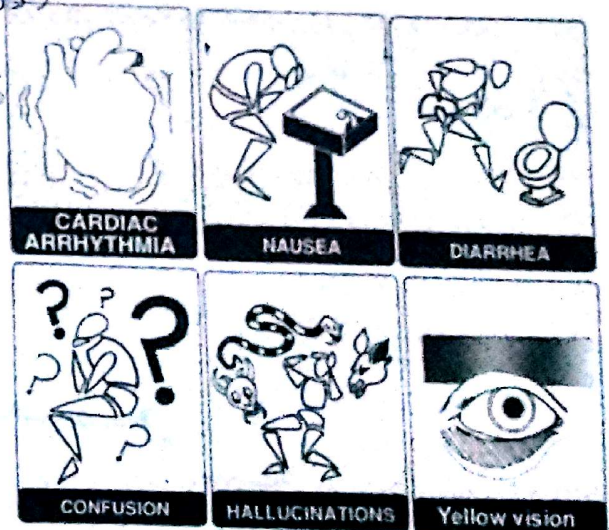
Predisposing factors

- Hypokalemia: Reduced plasma K^+ leads to increased phosphorylation of the Na^+/K^+ -ATPase, and this increases digoxin binding and effect. K and digitalis compete
- Hypercalcemia (N.B. Hypocalcemia renders digitalis less effective).
- Excessive digitalis therapy especially in elderly patients.
- Renal or hepatic impairment.

Manifestations

Cardiac

- brady arrhythmia
tachy ~
- Bradycardia and variable degree of heart block.
- Paroxysmal atrial tachycardia
- Any type of arrhythmia (e.g. ventricular premature beats, bigeminy, trigeminy, etc.)



Extracardiac:

- The first manifestation of overdose is fatigue and flu-like symptoms.
- GIT: anorexia, diarrhea, nausea & vomiting (due to stimulation of CTZ).
- CNS: headache, delirium, hallucination, and convulsions.

- Vision: yellow vision (chromatopsia), diplopia, amblyopia, scotoma, white borders surrounding dark objects, etc. due to retrobulbar neuritis
- ⊗ - Others: skin rash, gynecomastia, galactorrhea

Management

- Stop digitalis administration.
- Correct hypokalemia:
 - Stop drugs that cause hypokalemia (e.g. diuretics).
 - Give K⁺ either i.v. or oral (2 gm/4 h).
- Antiarrhythmic drugs:
 - tachy arr → Lidocaine (in ventricular arrhythmia): 1-2 mg/kg i.v. bolus then (1-2 mg/min i.v.i.)
 - brady arr → Phenytoin (in ventricular arrhythmia): 100 mg i.v.i.
 - Atropine: if there is bradycardia or heart block.
- Specific digitalis antibodies (Fab fragments) to bind digitalis and promote its renal clearance (the most specific therapy).

Other positive inotropic drugs

Dopamine and dobutamine: see ANS B₁ agonist

Phosphodiesterase (PDE) inhibitors (Cardiac bipyridines):

Inamrinone - Milrinone read 'em

- They inhibit PDE enzyme (type 3) → ↑ cAMP → ↑ Ca²⁺ influx in myocardial cells → ↑ myocardial contractility.
- ⊗ ▪ They have VD properties.
- ⊗ ▪ They are used only i.v. and only for acute heart failure.
- Adverse effects include: thrombocytopenia, cardiac arrhythmia increase liver enzymes (hepatotoxicity).
- Milrinone is less toxic than inamrinone

Notes

inam rinone
mil

Diuretics

Mechanism in heart failure

- They ↓ fluid retention and pulmonary congestion leading to improvement of tissue oxygenation
- They ↓ preload & afterload so improve myocardial function.
- **Spironolactone** antagonizes the effect of ^{anti}aldosterone that is increased in CHF due to secondary stimulation of RAAS.

Disadvantages of diuretics

- Excessive use of diuretics will ↓ ECF volume → ↓ COP.
- Diuretic-induced acid-base imbalance may impair cardiac function.
- Diuretic-induced hypokalemia can ↑ digitalis toxicity and cardiac arrhythmia.

These adverse effects could be minimized by **diuretic combination** (loop diuretics plus K⁺ sparing diuretics) to minimize hypokalemia and acid-base imbalance.

Vasodilators

Arterioldilators ↓ afterload while venodilators ↓ preload.

Indications in HF

- Left ventricular failure due to systemic hypertension, valvular heart disease, or complicating cardiac surgery.
- Right ventricular failure due to pulmonary hypertension.

- The ideal vasodilator in **acute HF** should have rapid onset and short duration e.g. Na nitroprusside.
- The ideal vasodilator in **chronic HF** should be effective orally and have long duration e.g. ACEIs or hydralazine.

ACEIs

Mechanism in heart failure

- They ↓ arterial BP → ↓ afterload.
- They ↓ aldosterone → ↓ Na & H₂O retention → ↓ preload.
- They prevent myocardial wall thickening and cardiac remodeling.

β-blockers

Although β-blockers are generally not recommended in heart failure (because they produce -ve inotropic effect and may precipitate cardiac decompensation), they may have some benefits in heart failure because most patients with HF have sympathetic overactivity (tachycardia). *Chronic*

Mechanism of β-blockers in heart failure:

- β-blockers reduce tachycardia → ↓ myocardial O₂ demand.
- β-blockers reduce BP → ↓ ventricular strain associated with HF.
- β-blockers inhibit renin release → ↓ cardiac remodeling caused by RAAS.
- Carvedilol is a new beta-blocker with additional VD and antioxidant properties.

Beta-blockers are specially indicated in the following cases

- HF associated with ↑ sympathetic overactivity.
- HF associated with pheochromocytoma.
- High output failure associated with thyrotoxicosis.

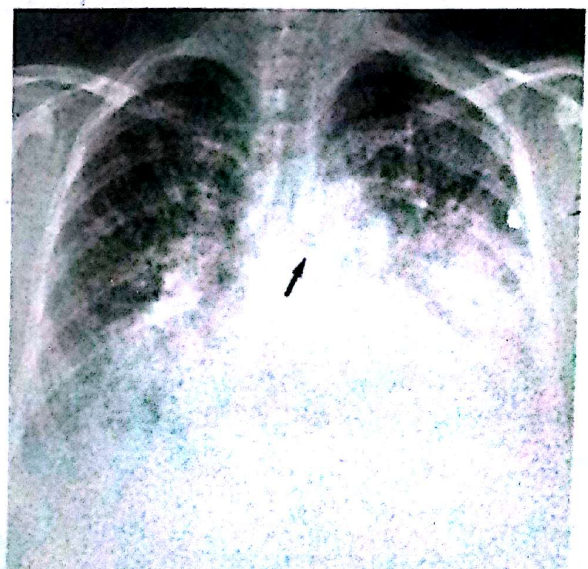
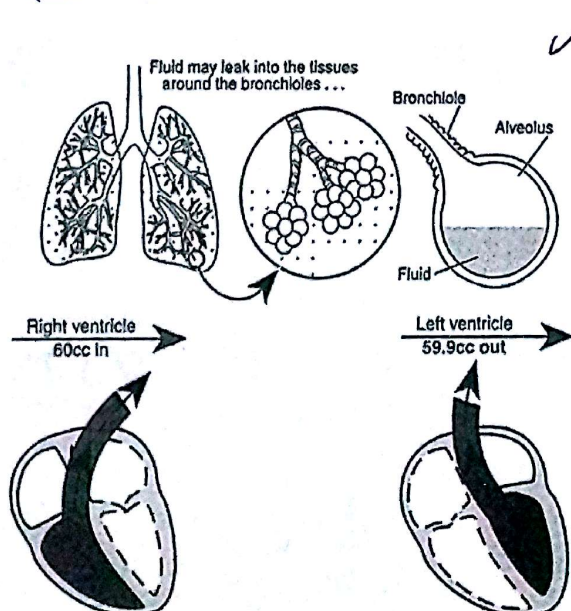
acute 11 20 2010



Management of acute (cardiogenic) pulmonary edema

Pathophysiology of APE

Acute cardiogenic pulmonary edema (APE) is accumulation of fluid (transudate) in the lung interstitium and alveoli as a result of increased capillary hydrostatic pressure secondary to LV dysfunction.



Manifestations

Dyspnea, orthopnea and wheezes.

* Chest x-ray shows patchy or diffuse alveolar filling (haziness).

Management

1. Hospitalization.

2. Semi-setting or sitting position.

3. Morphine: (5 mg i.v.)

- Analgesic effect → ↓ stress of the patient.

- Venodilatation → ↓ VR → ↓ lung congestion.

* It ↓ pulmonary stretch reflex → ↓ tachypnea & work of breathing.

- Inhibit respiratory centre.

4. Oxygen: by oxygen mask or even hyperbaric

oxygen. Oxygen will also reduce pulmonary capillary pressure & edema.

5. Vasodilators: Na-Nitroprusside (i.v.), or Nitroglycerine, Nifedipine (SL).

6. Aminophylline (250 mg slowly i.v.)

- It causes bronchodilatation.

- It ↑ myocardial contractility.

7. Loop diuretics: (furosemide i.v.) 40-80 mg i.v.

Diuretics ↓ venous return and pulmonary congestion.

It ↓ systemic BP (afterload).

8. Digoxin: (rapid digitalization) 0.25 mg (i.v.) provided that there are no contraindications.

9. Treatment of the cause: e.g. rapid rise of BP, atrial fibrillation, etc.

Notes

morphine is only giving in pulmonary edema due to LV failure



Part 4: Shock States and Their Management

Shock is a circulatory disorder. It is a complex state of hypotension and impaired tissues perfusion of vital organs (acute circulatory failure).

Diagnosis

- Systolic BP < 90 mmHg OR mean arterial BP (MAP) < 60 mmHg.
- Tachycardia and tachypnea
- Clinical manifestations of poor tissue perfusion:
 - Oliguria (urine < 20 ml/h), or anuria.
 - Cool pale extremities with slow capillary refilling.
 - Confusion and restlessness.

Anaphylactic shock

It is a medical emergency that requires immediate recognition and intervention.

Causes, manifestations, and time course

Acute hypersensitivity reaction in response to allergic substance (food, drugs or venom) → massive release of histamine from mast cells:

- Skin changes (the first feature): erythema, urticaria, or angioedema.
- Hypotension (fainting).
- Bronchoconstriction (wheeze or hoarse voice).
- Fatal food reactions typically occur after 30-35 minutes.
- Insect stings cause shock after 10-15 minutes.
- Intravenous medication reactions occur within 5 minutes.

Treatment

- Apply tourniquet proximal to the site of injection if possible.
- ① - Epinephrine (0.5 ml i.m.) (s.c. injection is slow).
 - It is the drug of choice and potentially lifesaving.
 - i.m. injection in the thigh (vastus lateralis) gives more rapid effect.
 - Repeat after 5 min if no response.
- 2 - Antihistamine (e.g. chlorpheniramine 10 mg i.v.)
- 3 - Hydrocortisone 200 mg i.v. to ↓ antigen/antibody reaction. + anti-inflammatory + salt and water retention
- Intravenous fluids (0.5-1 L) and monitor BP.

Neurogenic Shock

- Neurogenic shock is caused by loss of sympathetic tone of blood vessels resulting in the massive dilatation of arterioles and venules.
- It can be caused by general or spinal anesthesia, spinal cord injury, pain, and anxiety.

Treatment

- Recumbent position with head down.
- Sedatives. → Stress لا تقبله
- Vasopressor sympathomimetics.

Hypovolemic shock

Causes

- Blood loss (hemorrhage, internal or external).
- Plasma loss (severe burn).
- Water loss (vomiting, diarrhea).

Grades of hypovolemic shock

	Blood loss	Response
Class I	Up to 15% (750 ml)	Compensatory mechanisms maintain BP.
Class II	15-30% (750-1500 ml)	Hypoxia, hypotension, ↓ urine output
Class III	30-40% (1500-2000 ml)	Profound shock with <u>severe acidosis</u>
Class IV	> 40% (> 2000 ml)	Coma death

Treatment

I.v. fluids (Ringer solution is more superior to normal saline for use in massive hemorrhage).

- Blood transfusion
- Dopamine: to ↑ COP.
intermediate dose

+ vasopressors after restoration blood volume

Cardiogenic shock

Causes

- Acute MI
- Blunt cardiac trauma
- Myocardial depression due to any cause (drugs, infection, etc.).

Treatment

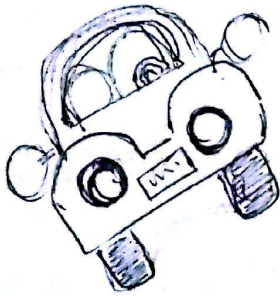
- All measures of treatment of acute MI (see page 128).
- Dobutamine i.v.i (usually at 5 - 20 $\mu\text{g/kg/min}$). *dopamine also*
- Lidocaine i.v. for control of ventricular arrhythmia.
- iv fluids

Septic shock

Cause: severe infection → release of inflammatory cytokines from the inflammatory cells → venodilatation (↓ venous return) and progressive tissue hypoxia.

Treatment

- Antibiotics according to the type of pathogen.
- Dopamine or dobutamine to ↑ COP.
- Low dose steroids to minimize toxemia.
- Oxygen



Notes

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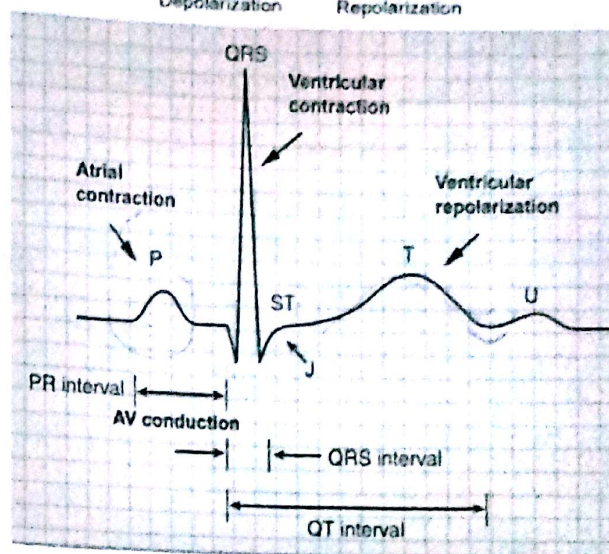
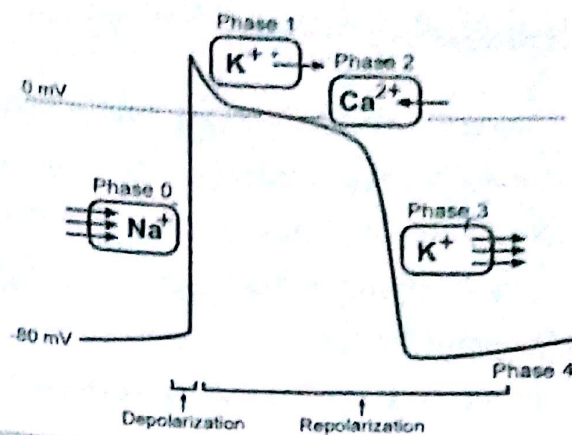
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Part 5: Cardiac arrhythmia and antiarrhythmic drugs

Basic electrophysiology

Cardiac action potential

- In the resting state, K^+ ions are found mainly intracellular, while Na^+ and Ca^{2+} are mainly extracellular making the interior of the cell electrically negative.
- Contraction and relaxation occur when rapid redistribution of ions across the cell membrane occurs during 4 phases known as "action potential".



phases of action potential:

- Phase 0:** rapid depolarization of the cell due to rapid influx of Na^+ .
- Phase 1:** short period of rapid re-polarization due to outflow of K^+ .
- Phase 2:** "plateau": delay in re-polarization due to slow influx of Ca^{2+} .
- Phase 3:** second period of rapid repolarization due to rapid out-flow of K^+ .
- Phase 4:** the resting state is restored. Na^+ ions are extruded out the cell and K^+ ions return back by the Na^+/K^+ pump and so on.
- The slope of phase 4 determines when the 2nd action potential starts. When the slope is increased, the distance between 2 cardiac cycles shortens (i.e. tachycardia) and vice versa.

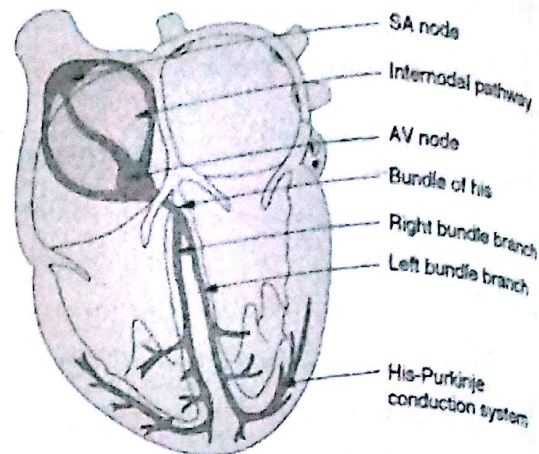
Impulse formation (automaticity)

- Cardiac **automaticity** refers to the ability of certain cells to self-generate electrical impulses that spread throughout the heart.
- Under normal conditions, the **SA node** is the dominant pacemaker (i.e. has the highest automaticity).
- Normal myocardial cells don't have automaticity i.e. cannot generate impulses.
- Under certain pathologic conditions, some myocardial cells may acquire automaticity.

spontaneous repetitive firing, this is called **abnormal automaticity** or **ectopy**. These **ectopic pacemakers** compete with the SA node for control of the heart.

Impulse conduction

- Electrical activity spreads from the **SA node** to the ventricles via the **AV node** and the **bundle of His**, and then down through the right and left bundles.
- In the ECG, the **P wave** represents the spread of depolarization wave through the atria (atrial contraction). The **QRS complex** represents the spread of depolarization wave through the ventricles (ventricular contraction). The ST segment and T wave represent ventricular repolarization (relaxation).



Cardiac arrhythmia

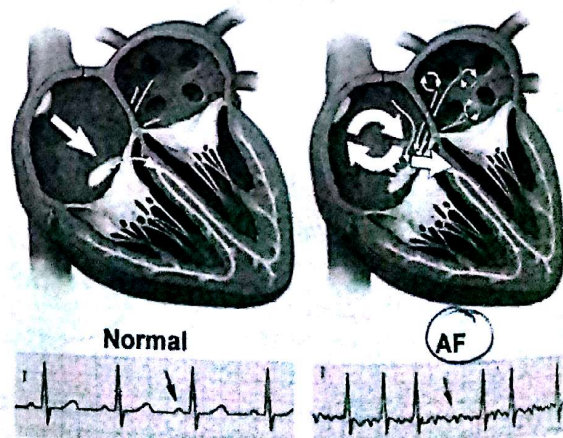
Arrhythmia means disturbance in the normal heart rhythm. It results from: (1) abnormal impulse generation; (2) abnormal impulse conduction or (3) both.

Abnormal impulse formation

- Nodal abnormality:** e.g. sinus tachycardia and sinus bradycardia.
- Extranodal abnormality:** e.g. premature atrial or ventricular contractions (ectopic beats).

Abnormal impulse conduction

- Re-entry:**
 - This is a circus movement of an impulse that circulates around certain area in a unidirectional fashion and excites the conducting system more than once.
 - It is the most common cause of



atrial flutter and fibrillation (AF).

Heart block:

AV conduction is delayed (first degree), intermittent (second degree), or completely blocked (third degree).

Wolff-Parkinson-White syndrome:

It is due to an accessory A-V conducting pathway, which conducts more rapidly than the normal pathway and one ventricle is excited before the other. Digitalis, and verapamil $\downarrow$ conduction in the normal pathway but $\uparrow$ it in the accessory pathway.

both $\downarrow$ HRP

Antiarrhythmic drugs

- Antiarrhythmic drugs are classified according to the modified Vaughan Williams classification system.
- This simplified system assumes that each drug has one main mechanism of action.

Class I: Na^+ channel blockers: e.g. quinidine

- Class IA: moderately block Na^+ channels and $\uparrow$ APD (action potential duration) e.g. quinidine and procainamide
- Class IB: weakly block Na^+ channels and $\downarrow$ APD e.g. lidocaine and phenytoin.
- Class IC: strongly block Na^+ and K^+ channels e.g. flecainide and propafenone.

Class II: Beta-blockers: e.g. propranolol

- They $\downarrow$ A-V conduction.
- They $\downarrow$ slope of phase 4 depolarization (i.e. $\downarrow$ spontaneous depolarization).
- Some BB has additional membrane stabilizing action e.g. propranolol.

Class III: K^+ channel blockers: e.g. amiodarone, sotalol

- They inhibit mainly K^+ channels and $\uparrow$ APD.

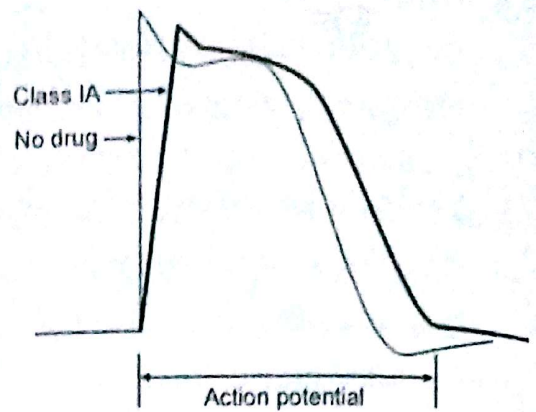
Class IV: Ca^{2+} channel blockers: e.g. verapamil and diltiazem

- They inhibit mainly Ca^{2+} channels and $\uparrow$ APD.

Class 1A: Quinidine

Mechanism of action

- It blocks Na^+ channels and $\uparrow$ action potential duration.
- $\downarrow$ slope of phase 4 depolarization.
- $\downarrow$ atrial conduction (direct effect) and $\uparrow$ A-V conduction (atropine-like action).
- It has -ve inotropic effect ($\downarrow$ contractility).



Therapeutic uses

- Supraventricular arrhythmia: atrial flutter, fibrillation and paroxysmal atrial tachycardia.
- Ventricular arrhythmia.

Side effects

- Cinchonism: ringing in the ears, blurred vision, nausea and vomiting.
- Embolism: due to dislodgment of atrial mural thrombus (see below).
- Paradoxical tachycardia: due to atropine-like action.
- Quinidine syncope: episodes of fainting associated with $\uparrow$ QT interval. It is due to polymorphic ventricular tachycardia "torsade de pointes".
 $\rightarrow$ due to ectopic focus

Contraindications and Precautions

- It should not be used to treat long standing AF (dated > 6 months). Why?
Because in old standing AF there may be a big mural thrombus in the atrium and if atrial contraction is corrected $\rightarrow$ fragmentation $\rightarrow$ cerebral embolism.
- Patient should be digitalized before quinidine. Why?
Quinidine has atropine-like action and if given alone, it $\uparrow$ A-V conduction and transmits the rapid atrial rate to the ventricles "paradoxical tachycardia".
Digitalis is given to $\downarrow$ A-V conduction and prevents this "paradoxical tachycardia".
- It should not be given to patients with prolonged QT syndrome. Why?
Quinidine $\uparrow$ APD (= prolong the QT interval) and predispose the patient to fatal polymorphic tachycardia "torsade de pointes".

Class II: Beta blockers

Mechanism of action: See before

Therapeutic uses

- Arrhythmia due to thyrotoxicosis.
- Arrhythmia associated with HOCM.
- Supraventricular arrhythmia.
- Arrhythmia due to mitral valve prolapse.

↓ A-V conduction

↓ slope

MSA → propranolol

regurgitation of blood from V to A

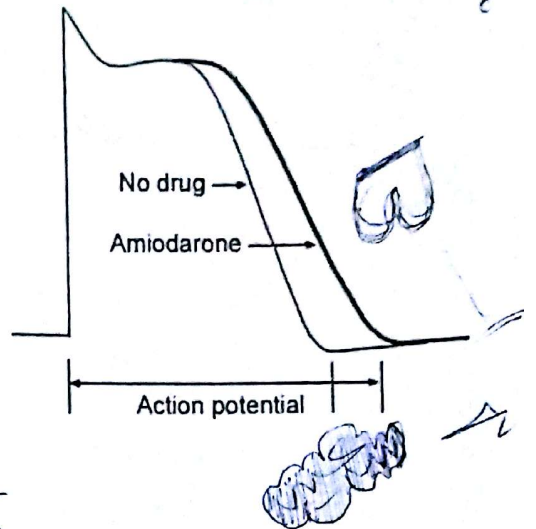
Shift

Class III: Amiodarone

(broad spectrum anti-arrhythmic)

Mechanism of action

- Blocks mainly K^+ channels → slowing of phase 3 → ↑ APD.
- Blocks Na^+ channels → ↓ excitability.
- Blocks Ca^{2+} channels → -ve inotropic and chronotropic effects.

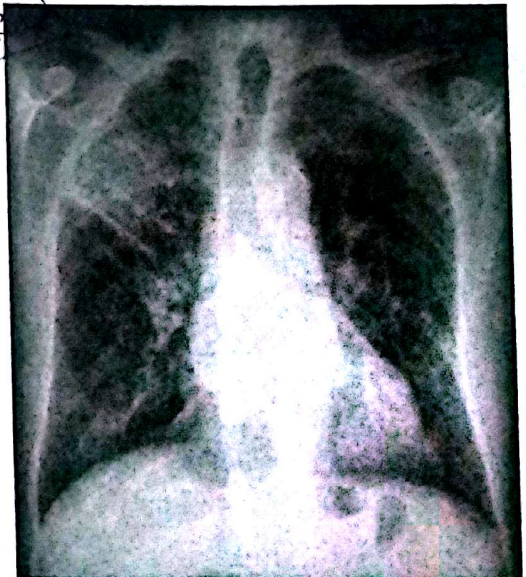


Therapeutic uses: Most types of arrhythmia:

- Supraventricular and ventricular arrhythmia.
- WPW syndrome. *use digoxin*
- Arrhythmia resistant to other drugs. *no BAs, no CCBs, no digoxin*

Side effects

- Corneal microdeposits: reversible, does not affect vision. *hypo*
- Thyroid dysfunction: because it is heavily iodinated. *hyper*
- Bradycardia and heart block.
- Pulmonary infiltration.
- Hepatic dysfunction.



Chest x-ray in an elderly patient on amiodarone demonstrates numerous reticular opacities most marked in the right upper zone

Class IV: CCBs; Verapamil, diltiazem

Mechanism of action: They ↓ SA node activity and AV conduction

Therapeutic uses: the same as beta-blockers

Other non-pharmacological methods

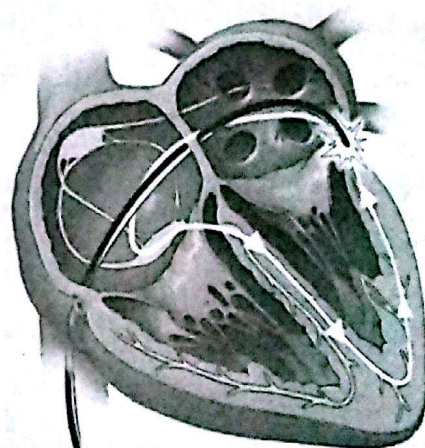
Cardioversion

- It is application of direct current (electric shock) to the chest wall for emergency control of any type of arrhythmia.
- It is the preferred method in emergencies.
- ~~X~~ Digitalis is contraindicated with cardioversion because it may predispose to cardiac arrest.



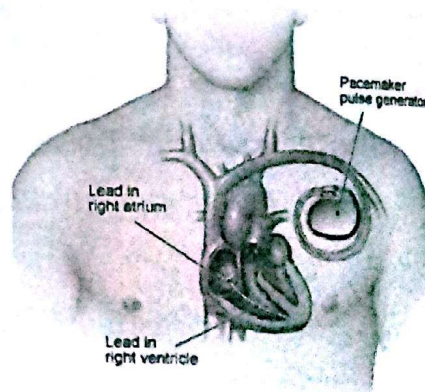
Laser ablation

- It is used for many types of arrhythmias.
- A catheter is inserted into a specific area of the heart. A special machine directs energy through the catheter to small areas of the heart muscle that causes the abnormal heart rhythm. This energy "disconnects" the pathway of the abnormal rhythm.
- It can also be used to disconnect the accessory pathway in WPW syndrome.



(Artificial pacemakers) and implantable cardioverter defibrillators

- They are battery-powered electronic devices that are implanted under the skin or in the chest cavity to monitor and pace the heart.



Notes

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